Effect on Mortality of Higher vs Lower Beta Blocker (Metoprolol Succinate or Carvedilol) Dose in Patients with Heart Failure

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Abstract

This study aimed to compare the effect of beta blocker dose and heart rate on mortality in patients with heart failure with reduced ejection fraction (HFrEF). The Veteran Affairs databases were queried to identify all patients diagnosed with HFrEF based on ICD-9 codes from 2007-2015 and beta blocker (carvedilol or metoprolol succinate) use. 36,168 patients on low dose beta blocker were then matched with 36,168 patients on high dose beta blocker using propensity score matching. The impact of beta blocker dose and heart rate was assessed on overall mortality using Cox proportional hazard model. After dividing average heart rate into separate quartiles and adjusting for patient characteristics, high beta blocker dose was associated with lower overall mortality as compared to a low dose of beta blocker (HR:0.75, 95% CI:0.73-0.77,p<0.01) independent of the heart rate achieved. The results held for all 4 quartiles of average heart rate. A higher beta blocker dose or a lower heart rate were both independently and jointly associated with lower mortality for all quartiles of heart rate. In conclusion, higher dose of beta blocker therapy and a lower achieved heart rate were both independently associated with a reduction in mortality in HFrEF patients.

Keywords: Heart failure with reduced ejection fraction, beta blocker, heart rate, veterans

As per current major societal guidelines, beta blocker therapy is indicated in the treatment all patients with heart failure with reduced ejection fraction (HFrEF) with left ventricular (LV) ejection fraction (EF) ≤ 0.40.(1-3) The 3 beta blockers currently approved for such patients are carvedilol, metoprolol succinate and bisoprolol. Of these, carvedilol and metoprolol succinate are the most commonly used in the United States. While a beta blocker can reduce the heart rate (HR), the benefit of these medications in HF patients may not be due entirely to their HR lowering mechanism.(4) Two meta-analyses suggested that HR reduction may be the major contributor to the clinical benefits of beta blocker therapy rather than target dose in systolic heart failure.(5, 6) Data from HF-ACTION trial showed that a higher beta blocker dose was associated with better outcomes regardless of baseline HR.(7) The relative importance of lowering HR compared to titrating dose to maximum tolerated levels remains unclear. In this large retrospective study, the aim was to determine the relative importance of lowering HR compared to beta blocker dose in reducing mortality in patients with HFrEF.

Methods

Data of patients diagnosed with HF either as an inpatient or an outpatient from January 1st 2007 to January 27th 2015 were retrieved from Veterans Affairs (VA) Corporate Data Warehouse (CDW) through the Veterans Administrations Informatics and Computing Infrastructure (VINCI). Patients who did not refill the beta blocker through a VA outpatient pharmacy and those who did not take the medication for >30 days were excluded. Follow up duration was defined as the interval from the initial VA outpatient pharmacy fill date to death or to the end of the study. Mortality data was obtained through the VA's death registry. All patient's comorbidities were based on inpatient or outpatient International Classification of Diseases 9th Revision (ICD-9) codes. Implantable cardioverter-defibrillator (ICD) implantation was defined by Current Procedural Terminology (CPT) codes and ICD-9 codes.

Patients with missing, inconsistent, or seemingly erroneous values in variables such as sex, treatment dates, death, HR, and average daily dose of beta blocker were removed. Patients who died within 30 days of treatment were excluded from the study. Patients who switched beta blocker therapy at any time were also excluded from the study.

Out of all the patients with HFrEF at the VA treated who did not cross over treatment 165,224 patients were reviewed. After removing patients due to missing data, duration of therapy <30 days, and average heart rate <45 bpm our sample size of patients (metoprolol succinate or carvedilol) during their treatment was 114,010 with 36,168 patients using a low dose and 77,842 patients using high dose of the beta blocker. Following Fiuzat et al., the beta blocker dose was classified as “High Dose Beta Blocker” for dose ≥25 mg of carvedilol daily (and ≥100 mg of metoprolol succinate.(7) “Low Dose Beta Blocker” was defined as those <25 mg carvedilol daily (or <100 mg metoprolol daily). In Figure 2, the sample was divided into 4 quartiles of average heart rate measured during treatment. The Cox proportional hazard models were performed after adjusting for clinical characteristics and medications listed in Table 1.

The beta blocker dose was a dependent variable, and it was used as propensity score matching with replacement method to reduce heterogeneity in baseline characteristics, average heart rate, and comorbidities. This method identified patients who were taking a low beta blocker dose that were comparable in their characteristics with high dose patients. The combinations of beta blocker dose and quartiles of heart rate were plotted using the Kaplan Meier survival estimate. Follow-up time and censored observations were analyzed by using Cox proportional hazard model to assess the effects of patients taking high doses of beta blocker on overall mortality. The robust standard errors were used for all our analysis. The matched sample was analyzed with and without adjustments of patient characteristics and comorbidities. Regression adjustment estimation technique was used on the matched data to estimate the

average treatment effect. Sub-sample analysis of metoprolol and carvedilol groups was performed to test if the dose on top of beta blocker had any differential impact on the overall mortality. The Cox proportional hazard models were separately analyzed using all 4 quartiles of heart rate. We also applied average treatment effect to the matched data using regression adjustment estimation technique, which takes the averages of predicted outcomes to measure the treatment effect. All statistical analyses were performed using STATA 15.1. A p value < 0.01 was considered statistically significant.

RESULTS

The average follow-up duration was 1192 days. Shown in Figure 2, the 1st, 2nd, 3rd, and 4th quartile average heart rate on treatment for the matched sample were 64 beats/min, 71 beats/min, 77 beats/min, and 87 beats/min respectively.

From the total sample, 36,168 of low dose beta blocker patients were matched with as many high dose beta blocker patients. Table 1 shows the average baseline characteristics of sample taking either metoprolol succinate or carvedilol beta blocker by dose before and after matching. The characteristics appear to be statistically different across beta blocker dose before matching. However, after matching almost all the covariates were not statistically different from each other between low and high beta blocker dose.

Figure 1 illustrates the Kaplan Meier survival estimate plots of high versus low beta blocker dose, with a higher survival rate in patients on a high dose beta blocker. Figure 2 shows the Kaplan Meier survival estimate plots of heart rate quartiles on our matched sample. Patients with a lower heart rate had a higher survival rate. Figure 3 shows the Kaplan Meier survival plots of beta blocker dose by quartiles of average heart rate on treatment. The patients with a lower heart rate while taking a high dose beta blocker had better survival.

Table 2 shows the unmatched and matched hazard ratio of beta blocker dose and also by type of beta blocker on mortality. Patients on a high dose of beta blocker were associated with lower overall mortality as compared to a low dose of beta blocker (HR: 0.74, 95% CI: 0.73-0.76, p <0.01). The results were consistent even after adjusting for patient characteristics and comorbidities (HR: 0.75, 95% CI: 0.73-0.77, p<0.01). They remained consistent for both metoprolol succinate (HR: 0.88, 95% CI: 0.85-0.91, p<0.01) and carvedilol (HR: 0.65, 95% CI: 0.63-0.67, p<0.01) with average daily dose of 103mg and 18mg respectively. The improved survival of carvedilol over metoprolol succinate is consistent to our previous study.(8)

From the treatment effects model, we find that the estimated average time to mortality when all matched sample were treated using low dose was 6.6. When the entire matched sample were treated with high dose of beta blocker, the average time to death was estimated to increase by 1.35 years (or 20% increase) than when all matched sample were treated using low dose of beta blocker.

Table 3 shows the relative hazard ratios across different combinations of beta blocker dose and heart rate quartiles after adjusting for age, sex, and comorbidities. For the unadjusted columns in the table, the baseline (HR=1) was defined as patients with high beta blocker dose and in first quartile of heart rate. The higher the heart rate quartile was correlated with greater relative hazard. Higher beta blocker doses resulted in lower hazard compared across all quartiles of heart rate. These findings were consistent after adjusting for age, sex, comorbidities, and medications. Figure 4 shows the box-plot graph of the beta blocker dose versus heart rate quartiles. The higher beta blocker dose and lower heart rate were both independently and jointly associated with lower mortality for all quartiles of heart rate.

Discussion

There are several significant findings from our study. First, in patients with HFrEF use of high dose of beta blocker (either carvedilol or metoprolol succinate) was associated with improved survival. Second, a lower heart rate on treatment was also associated with lower mortality. But even in patients who achieved lower heart rates, a higher beta blocker dose was independently associated with lower mortality. Thus, higher beta blocker dose was additive to heart rate lowering in reducing long term mortality in HFrEF and was independently associated with better survival irrespective of heart rate lowering.

Although current guidelines recommend up titration of beta blocker therapy to moderate to high doses (1, 2), patients in the real world practice and also in clinical trials remain often under target.(7, 9) An analysis of the COMET showed that beta blocker dose as well as heart rate achieved on beta blocker were independently associated with outcomes.(10) However, in real-life situations, the dose of beta blocker used was frequently sub-optimal as shown by the data from the OPTIMIZE-HF registry.(11)

Two studies have shown better clinical outcomes with higher doses of angiotensin converting enzyme or angiotensin receptor blockers.(12, 13) However, there has been little evidence that beta blocker dose effects clinical outcomes in HF patients**.**(10, 14, 15) Improved outcomes with higher doses of beta blocker could be related to greater antagonism of the neurohormonal system, as long-term activation of sympathetic nervous system leads to deleterious effects on cardiac function.(16) However, the negative results of a large trial using moxonidine, which inhibits sympathetic activation, may cast doubt on this hypothesis.(17) Interestingly, ivabradine which decreases heart by blocking I_f channel rather than sympathetic inhibition did not reduce overall mortality when it was added.(18)

In contrast to McAlister et al.'s meta-regression analysis of beta blockers in HF trials which demonstrated that the magnitude of survival benefit seen with beta blockers was

associated with the heart rate reduction achieved rather than the dose.(5) Our study demonstrated survival benefit with both heart rate reduction and high beta blocker dose similar to recent meta-analysis by Kotecha et al. that demonstrated beta blocker dose and achieved target heart rate reduced mortality in HFrEF in sinus rhythm.(19)

The benefits of beta blocker dose have been shown to be dose dependent in the REVERT trial which examined the effects of beta blocker therapy on LV remodeling in asymptomatic patients. The benefit of LV end-systolic volume index and LVEF were beta blocker dose-dependent.(14) Also, the MOCHA study demonstrated that higher doses of beta blocker lead to greater improvement in left ventricular ejection fraction and improved survival.(15)

Our results were consistent with a recent post-hoc analysis of the HF-ACTION trial, which showed that a higher beta blocker dose was associated with a lower combined endpoint of HF hospitalization and death than with reduced heart rate.(7) In addition, this study demonstrated that the benefit of heart rate reduction may be independent of the beta blocker dose. In contrast to our analysis which included only veterans, the authors had only ambulatory patients and excluded patients who were not medically stable. Additionally, changes in beta blocker dose and heart rate during follow up were not captured in the study.

The strengths of our study were that it was a nationwide analysis, large number of patients, long follow up and involvement of all patients who receive their care through the VA. Study limitations were those that apply to any retrospective analysis in which all confounders cannot be accounted for. Although all subjects had assumed LVEF ≤ 40%, given VA restrictions on these medications along with ICD9 diagnosis of HFrEF and similar rates of ICD implantation, individual LVEF were not obtained reliably from the database so validation of this

assumption was not possible. Also being a study done in the VA system, women were underrepresented.

In conclusion, our study identified that beta blocker dose is associated with improved survival independent of achieved HR. The data suggests that up-titration of beta blocker dose and heart rate deduction should be aggressively targeted in patients with HFrEF.

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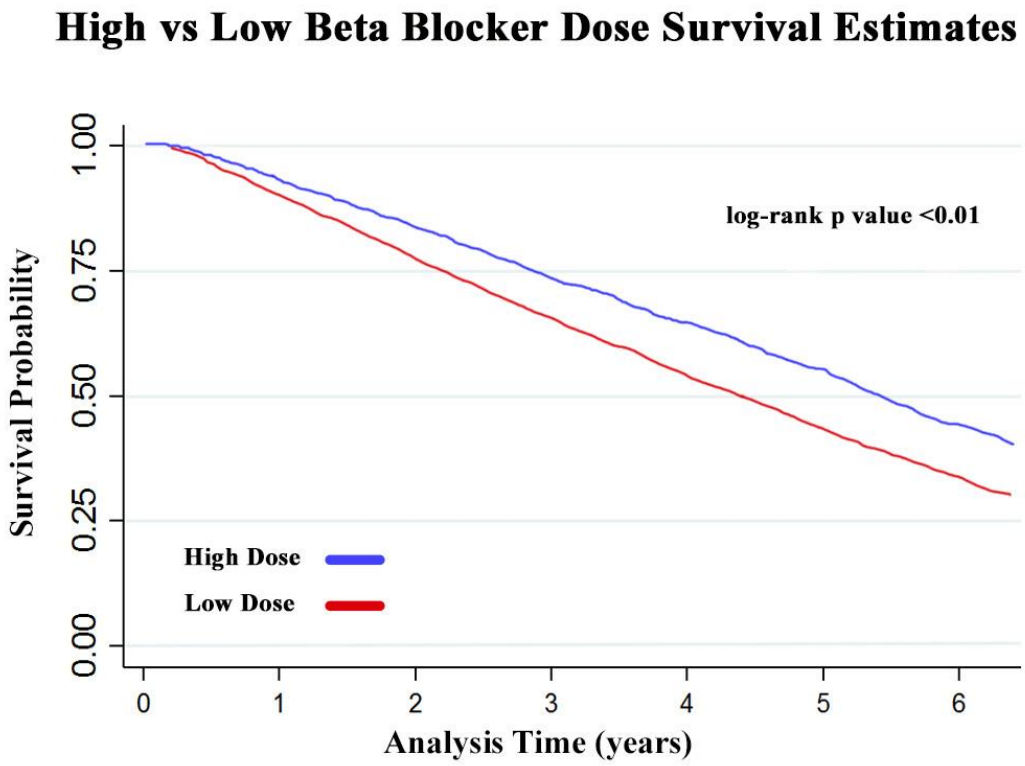
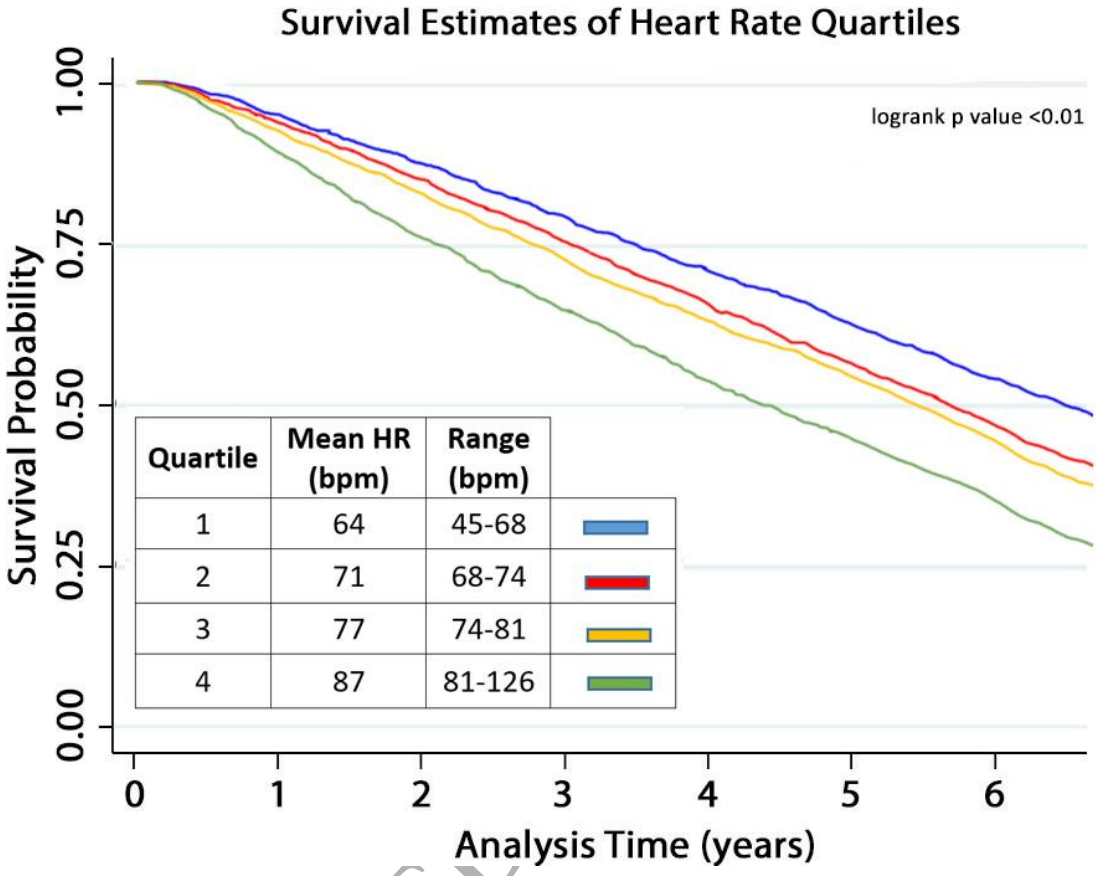
Figure 1: Kaplan Meier Survival Estimates: High versus Low Beta Blocker dose on Matched Sample



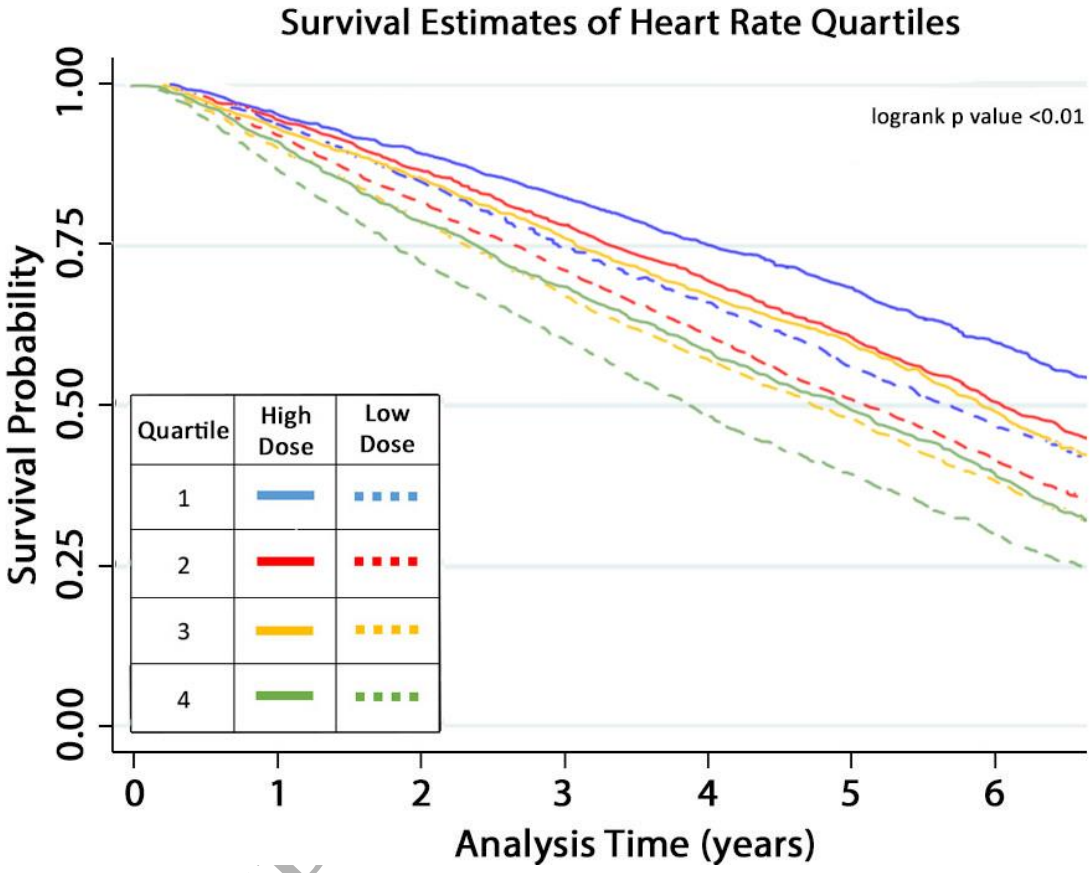
Note: Matched on quartiles of heart rate, age, sex, comorbidities, and medications

Figure 2: Kaplan Meier Survival Estimates of Heart Rate Quartiles on Matched Sample



Note: Matched by beta blocker dose, age, sex, comorbidities, and medications

Figure 3: Kaplan Meier Survival Estimates: Beta Blocker Dose and Between Quartiles of Average Heart Rate on Matched Sample



Note: Matched by quartiles of heart rate, beta blocker dose, age, sex, comorbidities, and medications

Figure 4: Relative Hazard Ratios by Heart Rate Quartile and Beta Blocker Dose on Matched Sample. Matched by quartiles of heart rate, beta blocker dose, age, sex, comorbidities, and medications

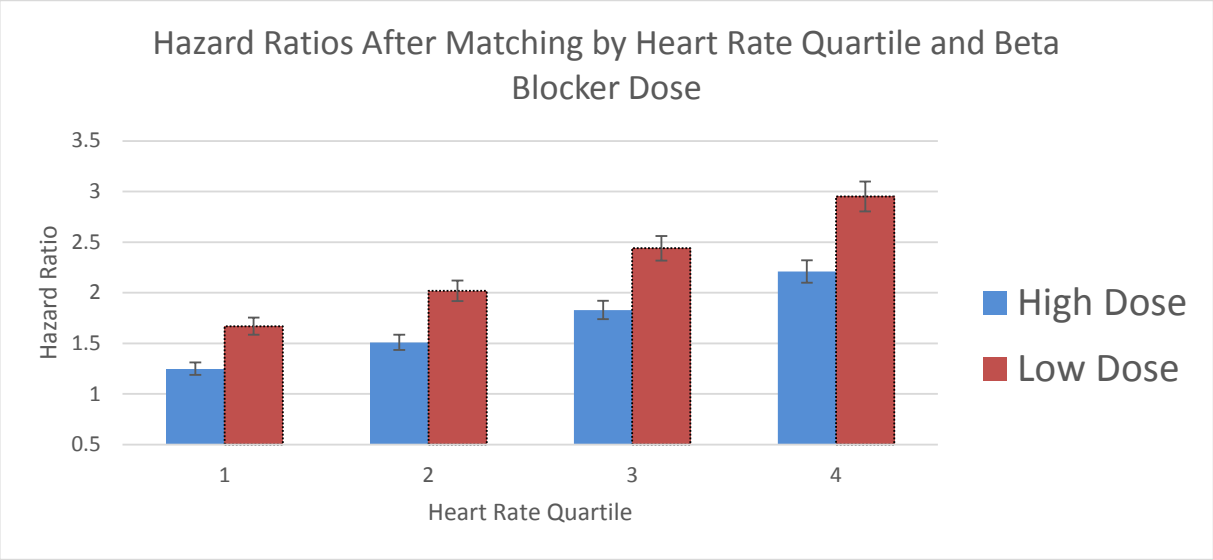


Table 1: Patient Characteristics by Beta Blocker (BB) Dose before and after Matching

	Pre-matching			Post-Matching		
Variable	**Low BB Dose**	**High BB Dose**	**p value**	**Low BB Dose**	**High BB Dose**	**p value**
Total	(n=36,168)	(n=77,842)		(n=36,168)	(n=36,168)	
Age(years)	71.47	66.82	<0.01	71.47	71.40	0.42
Women	2%	2%	<0.01	2%	2%	0.83
ICD	19%	25%	<0.01	19%	18%	0.22
Atrial fibrillation	34%	35%	<0.01	34%	34%	0.08
Coronary artery disease	61%	66%	<0.01	61%	61%	0.21
Chronic kidney disease	31%	41%	<0.01	31%	31%	0.96
Chronic obstructive pulmonary disease	33%	31%	<0.01	33%	32%	0.03
Cerebrovascular accident	12%	12%	<0.01	12%	16%	0.99
Cirrhosis	2%	2%	<0.01	2%	2%	0.65
Deep vein thrombosis	5%	5%	0.14	5%	5%	0.87
End stage renal disease	4%	7%	<0.01	4%	4%	0.12
Hypertension	61%	69%	<0.01	61%	60%	0.01
Obstructive sleep apnea	12%	20%	<0.01	12%	12%	0.54
Peripheral arterial disease	23%	24%	<0.01	23%	23%	0.09
Pulmonary embolism	3%	3%	0.18	3%	3%	0.62
Smoking	24%	25%	<0.01	24%	24%	0.76
Diabetes Mellitus	34%	63%	<0.01	34%	34%	0.67
Medications						
Loop Diuretic	73%	81%	<0.01	73%	73%	0.61
$P2Y_{12}$ inhibitor	37%	44%	<0.01	37%	36%	0.04
Eplerenone/Spironolactone	25%	36%	<0.01	25%	25%	0.30
Anticoagulant	32%	36%	<0.01	32%	32%	0.69
ACE inhibitor/ARB	90%	95%	<0.01	90%	90%	0.14
Calcium Channel Blocker	36%	49%	<0.01	36%	36%	0.73
Statin	87%	91%	<0.01	87%	86%	0.03
Digoxin	21%	26%	<0.01	21%	21%	0.83
Nitrate	27%	37%	<0.01	27%	27%	0.20
Hydralazine	9%	21%	<0.01	9%	9%	0.48
Aspirin	59%	62%	<0.01	59%	58%	0.02

Table 2: Cox Proportional Hazard Ratio with Likelihood of Survival of High Dose Beta Blocker Compared to Low Dose on Matched Sample

Sample	Unadjusted			Adjusted		
	Hazard Ratio	95% CI	p value	Hazard Ratio	95% CI	p value
Overall Sample	0.74	0.73-0.76	<0.01	0.75	0.73-0.77	<0.01
Metoprolol sample only	0.91	0.88-0.94	<0.01	0.88	0.85-0.91	<0.01
Carvedilol sample only	0.64	0.62-0.66	<0.01	0.65	0.63-0.67	<0.01

Note: Adjusted for quartiles of heart rate, age, sex, comorbidities, and medications

Table 3: Hazard Ratio by Heart Rate Quartile and Beta Blocker Dose. The baseline hazard ratio is quartile 1 and matched by age, sex, comorbidities, and medications.

		Unadjusted			Adjusted		
Quartile	Mean HR	High Dose (CI)	Low Dose (CI)	p value	High Dose (CI)	Low Dose (CI)	p value
1	64	1 (-)	1.34 (1.31-1.37)	<0.01	1.25 (1.19-1.31)	1.67 (1.57-1.76)	<0.01
2	71	1.20 (1.19-1.21)	1.61 (1.57-1.65)	<0.01	1.51 (1.43-1.59)	2.02 (1.90-2.13)	<0.01
3	77	1.44 (1.41-1.47)	1.94 (1.88-2.00)	<0.01	1.83 (1.73-1.93)	2.44 (2.29-2.59)	<0.01
4	87	1.73 (1.68-1.79)	2.33 (2.24-2.42)	<0.01	2.21 (2.08-2.34)	2.95 (2.76-3.15)	<0.01